SYNTHETIC METHODS FOR 2-AMINOALKYL PYRIDINES

BY

JOHN MIRZA

A.B., DePauw University, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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R. UNIV. BIBLIOTHEEK LEIDEN

SYNTHETIC METHODS FOR 2-AMINOALKYL PYRIDINES

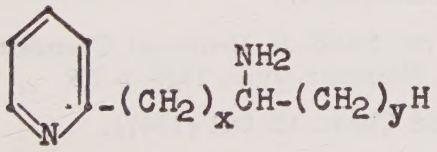
Introduction

In a search for compounds whose analgesic activity is somewhere between that of aspirin and that of types which cause addiction, other investigators have prepared aralkylamines with the amino group on the fourth or fifth carbon atom from the benzene ring. Several of these amines exhibited marked analgesic activity.[1]

2-Pyridyl isopropylamines have also been prepared in recent studies, and have been tested for analgesic properties.[2] It was of interest, therefore, to develop methods of synthesis for a group of five new 2-aminoalkyl pyridines carrying the amino group on the third, fourth, or fifth carbon atom from the pyridine nucleus.

Discussion

Various methods for the syntheses of five new 2-aminoalkyl pyridines represented by Structures I-V have been investigated.



I : x = 2; y = 0
II : x = 2; y = 1
III : x = 2; y = 2
IV : x = 3; y = 0
V : x = 4; y = 0

The prefered methods of synthesis for these compounds are summarized below.

1-(2-Pyridyl)-3-aminopropane (I) was synthesized by two routes: (1) β-(2-Pyridyl)-propionitrile was prepared from 2-vinylpyridine by a new method.[3] This compound was then catalytically reduced to the amine in yields of 92 per cent. (2) 3-(2-Pyridyl)-propanol was aminated by means of liquid

ammonia and Raney nickel at high temperatures.

1-(2-Pyridyl)-3-aminobutane (II) was synthesized by reductive amination of 1-(2-pyridyl)-3-butanone obtained by the treatment of β-(2-pyridyl)-propionitrile with methylmagnesium iodide or methyllithium. The same reaction involving the use of ethylmagnesium bromide failed to provide 1-(2-pyridyl)-3-pentanone, the intermediate for Compound III; the preferred reagent should be ethyllithium.

1-(2-Pyridyl)-4-aminobutane (IV) was prepared by a series of four steps: 2-Vinylpyridine was condensed with ethyl cyanoacetate.[4,5] The ethyl 2-cyano-4-(2-pyridyl)-butyrate thus obtained was saponified to give 2-cyano-4-(2-pyridyl)-butyric acid, which was decarboxylated to yield 4-(2-pyridyl)-butyronitrile. Catalytic reduction of this nitrile afforded the desired amine.

Attempts to alkylate ethyl cyanoacetate with 3-(2-pyridyl)-propyl bromide and with 3-(2-pyridyl)-propyl *p*-toluenesulfonate were shown to be unsuccessful methods for the preparation of ethyl 2-cyano-5-(2-pyridyl)-valerate, which is an intermediate for the synthesis of Compound V.

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VITA

The author was born in Bagdad, Iraq, on December 1, 1922, and came to the United States with his parents in May, 1929. He received his grammar school education in the public schools of Gary, Indiana, and was graduated from Horace Mann High School of that city in June, 1940. He entered DePauw University in September, 1940, and was granted the degree of Bachelor of Arts by that institution in November, 1943. From January, 1944, until February, 1946, he served in the United States Army. He entered the Graduate College of the University of Illinois in March, 1946. During the course of his graduate studies, he was employed as part-time teaching assistant.

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